# CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 40-371

## **APPROVAL LETTER**

DEC 29 2000

Watson Laboratories, Inc. Attention: Ernie Lengle, Ph.D. 311 Bonnie Circle Corona, CA 92880

#### Dear Sir:

This is in reference to your abbreviated new drug application dated May 7, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Oxycodone and Acetaminophen Tablets USP, 7.5 mg/500 mg and 10 mg/650 mg.

Reference is also made to your amendments dated September 11, and November 30, 2000.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Oxycodone and Acetaminophen Tablets USP, 7.5 mg/500 mg, and 10 mg/650 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drugs (Percocet® Tablets, 7.5 mg/500 mg, and 10 mg/650 mg, respectively, of Endo Pharmaceuticals, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Gary Buehler

Acting Director

Office of Generic Drugs

Center for Drug Evaluation and Research

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: 40-371

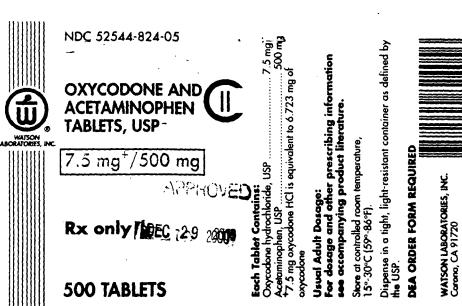
## **APPROVED DRAFT LABELING**

10-371 12/29/00 Labeling

Lot No.

52544-824-0

Z n



Last No.

Last N



## OXYCODONE AND ACETAMINOPHEN TABLETS, USP (1)



#### DESCRIPTION

Each tablet, for oral administration, contains:

Oxycodone hydrochloride	5 mg
Acetaminophen, USP	
Oxycodone hydrochloride	7.5 mg
Acetaminophen, USP	500 mg
Oxycodone hydrochloride	10 mg
Acetaminophen USP	650 mg

APPROVED DEC 29 2000

In addition, each tablet also contains the following inactive ingredients: colloidal silicon dioxide, crospovidone, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch and stearic acid.

The 7.5 mg/500 mg tablets and 10 mg/650 mg tablets also contain com starch and croscarmeilose sodium.

Oxycodone, 14-hydroxydihydrocodeinone, is a semisynthetic opioid agonist which occurs as a white, odorless, crystalline powder having a saline, bitter taste. It is derived from the opium alkaloid thebaine, and may be represented by the following structural

#### C18H21NO4.HCI

Molecular Weight = 351.83

Acetaminophen, 4'-hydroxyacetanilide, is a non-opiate, non-saticylate analogsic and antinyretic which occurs as a white, odorless, crystalline powder with a slightly bitter taste. It may be represented by the following structural formula:

#### CaHaNO<sub>2</sub>

Molecular Weight = 151.17

#### **CLINICAL PHARMACOLOGY**

The principal ingredient, exycodone, is a semisynthetic opioid analogsic with multiple actions qualitatively similar to those of morphine; the most prominent of these involve the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value of the exycodone in this product are analgesia and sedation.

Oxycodone is similar to codeline and methadone in that it retains at least one-half of it; analgesic activity when administered grafty.

Acetaminophen is a non-opiate, non-salicytate analgesic and antipyretic.

#### INDICATIONS AND USAGE

Oxycodone and acetaminophen tablets are indicated for the relief of moderate to moderately severe pain.

#### CONTRAINDICATIONS

Oxycodone and acetaminophen tablets should not be administered to patients who are hypersensitive to oxycodone or acetaminophen, or any other components of this product.

#### WARNINGS

Orug Dependence: Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of oxycodone and acetaminophen tablets, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral opioid-containing medications. Like other opioid-containing medications, oxycodone and acetaminophen tablets are subject to the Federal Controlled Substances Act (Schedule II).

#### PRECAUTIONS

#### General

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of opioids and their capacity to elevate cerebrospinal fluid pressure may be mankedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, opioids produce adverse reactions which may obscure the clinical course of patients

Acute-Abdominal Conditions: The administration of products containing exycodone or other optoids may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special Risk Patients: Oxycodone and acetaminophen should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using oxycodone and acetaminophen tablets should be cautioned accordingly.

Patients receiving other opioid analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (Including alcohol) concomitantly with oxycodone and acetaminophen may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

The concurrent use of anticholinergies with opioids may produce paralytic iteus.

Usage in Pregnancy

Teratogenic Effects: Pregnancy Category C: Animal reproductive studies have not been conducted with oxycodone and acetaminophen. It is also not known whether oxycodone and acetaminophen can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Oxycodone and acetaminophen should not be given to a pregnant woman unless in the judgment of the physician, the potential benefits outweigh the possible hazards.

Nonteratogenic Effects: Use of opioids during pregnancy may produce physical dependence in the neonate.

#### Labor and Delivery

As with all opioids, administration of oxycodone and acetaminophen to the mother shortly before delivery may result in some degree of respiratory depression in the newborn and the mother, especially if higher doses are used.

#### Nursing Mothers

ther oxycodone and acetaminophen are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when oxycodone and acetaminophen are administered to a nursing woman.

#### Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

#### **ADVERSE REACTIONS**

The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if - the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation, skin rash and pruritus. At higher doses, oxycodone has most of the disadvantages of morphine including respiratory depression.

#### DRUG ABUSE AND DEPENDENCE

Oxycodone and acetaminophen tablet is a Schedule II controlled substance.

Oxycodone can produce drug dependence and has the potential for being abused, (See WARNINGS).

#### OVERDOSAGE

#### Aceteminophes

Signs and Symptoms: In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma and thrombocytopenia may also occur.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams and fatalities with less than 15 grams. Importantly, young children seem to be more resistant than adults to the hepatotoxic effect of an acetaminophen overdose. Despite this, the measures outlined below should be initiated in any adult or child suspected of having ingested an acetaminophen overdose.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, yomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion

Treatment: The stomach should be emptied promotly by lavage or by induction of emests with syrup of ipecac. Patient's estimates of the quantity of a drug ingested are notoriously unreliable. Therefore, if an acetaminophen overdose is suspected, a serum acetaminophen assay should be obtained as early as possible, but no sooner than four hours following ingestion. Liver function studies should be obtained initially and repeated at 24-hour intervals.

The antidote. N-acety/cysteine, should be administered as early as possible, preferably within 18 hours of the overdose ingestion for optimal results, but in any case, within 24 hours. Following recovery, there are no residual, structural, or functional hepatic abnormalities.

#### Oxycodone

Signs and Symptoms: Serious overdosage with oxycodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy sidn, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Treatment: Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The opioid antagonist naioxone hydrochloride is a specific antidote against respiratory depression which may result from overdosage or unusual sensitivity to opioids, including oxycodone. Therefore, against respiratory or pression with a control to the control of t

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

Gastric emptying may be useful in removing unabsorbed drug.

#### DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of opioids. Oxycodone and acetaminophen tablets are given orally. The usual adult dosage is one tablet every 6 hours as needed for pain. The total daily dose of acetaminophen should not exceed 4 grams and the maximal daily dose is as follows:

	Maximal Daily Dose
5 mg / 325 mg	12 tablets
7.5 mg / 500 mg	8 tablets
10 mg / 650 mg	6 tablete

#### HOW SUPPLIED

Oxycodone and acetaminophen tablets, USP (5 mg oxycodone hydrochloride and 325 mg acetaminophen) are white, scored, round tablets debossed WATSON on one side and plain and scored on the other side. They are available as:

	Mark III	TOUR DESCRIPTION	
	Bottles of 100	52544-749-01	
	Bottles of 500	52544-749-0 <b>5</b>	
cetaminophen	tablets, USP (7.5 mg oxycod	one hydrochloride and 500 mg a	cetaminophen) are scored white,

Oxycodone and ac capsule shaped tablets debossed WATSON on one side and plain and scored on the other side. They are available as:

SIZE	WATSON NDC NUMBER
Bottles of 100	52544-824-01
Bottlee of 500	52544-824-05

Oxycodone and acetaminophen tablets, USP (10 mg oxycodone hydrochloride and 650 mg acetaminophen) are scored white, capsule shaped tablets debossed  $^{\mathrm{WATSON}}_{825}$  on one side and plain and scored on the other side. They are available as:

SIZE	WATSON NOC NUMBER
Bottles of 100	52544-825-01
Rottles of 500	52544-825-05

Store at controlled room temperature 15°C-30°C (59°F-86°F). [See USP]. Protect from moisture.

Dispense in a tight, light-resistant container as defined by the USP.

DEA Order Form Required.

Watson Laboratories, Inc.

Corona, CA 92880

Revised: Jan. 2000

# CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 40-371

**CHEMISTRY REVIEW(S)** 

# Food and Drug Administration Center for Drug Evaluation and Research Office of Generic Drugs Abbreviated New Drug Application Review

## 1. CHEMISTRY REVIEW NO. 3

- 2. ANDA #40-371
- 3. NAME AND ADDRESS OF APPLICANT
  Watson Laboratories, Inc.
  311 Bonnie Circle
  Corona, CA 92880

#### 4. LEGAL BASIS FOR SUBMISSION

RLD is Percocet® Tablets USP manufactured by ENDO Pharmaceuticals, ANDA 40-341. A citizen's petition for these two strength (7.5 mg/500 mg and 10 mg/650 mg) was filed by Endo and approved by the FDA on 11/6/98 (Docket No. 98P-0105/CP1).

All patents and exclusivities for the drug substance, drug product, dosing schedule, use, and indications have expired.

- 5. SUPPLEMENT(s)
  N/A
- 6. PROPRIETARY NAME
  N/A

- 7. NONPROPRIETARY NAME
  Oxycodone and
  Acetaminophen Tablets
- 8. SUPPLEMENT(s) PROVIDE(s) FOR:
- 9. AMENDMENTS AND OTHER DATES:

Firm:

May 7, 1999. Original submission

June 7, 1999 New correspondence (Labeling)
March 17, 00 Amendment (Chem and Labeling)

September 11, 00 Amendment facsimile

FDA:

June 3, 1999 Telecom (N. Mahmud)
June 23, 1999 Receipt acknowledgement

July 7, 99 Bio review adequate

November 29, 99 Chemistry Review 1-deficient

August 14, 00

Facsimile deficiencies

10. PHARMACOLOGICAL CATEGORY Narcotic analgesics

11. R or OTC

12. RELATED IND/NDA/DMF(s)

NDA 85-106 ANDA 40-341

DMFs

cap Liner

13. DOSAGE FORM

Tablets

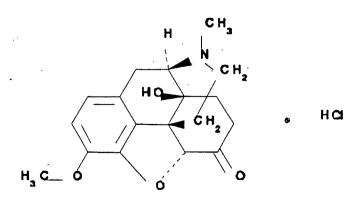
14. POTENCIES 7.5 mg/500 mg &

10 mg/650 mg

### 15. CHEMICAL NAME AND STRUCTURE

Oxycodone Hydrochloride

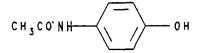
C<sub>18</sub> H<sub>21</sub> NO<sub>4</sub> . HCl



4,5 $\alpha$ -Epoxy-14-hydroxy-3-methoxy-17-

methylmorphinan-6-one hydrochloride

Acetaminophen USP C<sub>8</sub>H<sub>9</sub>NO<sub>2</sub>; M.W. = 151.17



4'-Hydroxyacetanilide

- 16. <u>RECORDS AND REPORTS</u>
  Labeling acceptable 10/2/00 by C. Park.
- 17. <u>COMMENTS</u> None.
- 18. <u>CONCLUSIONS AND RECOMMENDATIONS</u>
  Recommend approvable letter to issue.

19. REVIEWER:

Edwin Ramos

DATE COMPLETED:
November 5, 2000

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Commercial/Confidential

Information and are not releasable.

Men Per 3 11/5/2000

# Food and Drug Administration Center for Drug Evaluation and Research Office of Generic Drugs Abbreviated New Drug Application Review

- 2. ANDA #40-371
- 3. NAME AND ADDRESS OF APPLICANT
  Watson Laboratories, Inc.
  16600 NW 54<sup>th</sup> Ave.
  Miami, FL 33014
- 4. LEGAL BASIS FOR SUBMISSION

Percocet® Tablets USP ENDO Pharmaceuticals ANDA #40-341

A citizen's petition for these two strength (7.5 mg/500 mg10 mg/650 mg) was filed by Endo and approved by the FDA on 11/6/98 (Docket No. 98P-0105/CP1).

All patents and exclusivities for the drug substance, drug product, dosing schedule, use, and indications have expired.

- 5.  $\frac{\text{SUPPLEMENT}(s)}{N/A}$
- 6. PROPRIETARY NAME
  N/A

- 7. NONPROPRIETARY NAME
  Oxycodone and
  Acetaminophen Tablets
- 8. SUPPLEMENT(s) PROVIDE(s) FOR:
- 9. AMENDMENTS AND OTHER DATES:

Firm:

May 7, 1999: Original submission (subject of this review) June 7, 1999: New correspondence (Labeling)

Agency:

June 3, 1999: Telephone conversation (N. Mahmud) June 23, 1999: Receipt acknowledged.

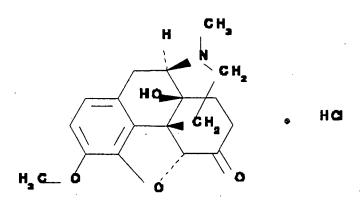
- 10. PHARMACOLOGICAL CATEGORY
  Narcotic analgesics

  11. R or OTC
- 12. RELATED IND/NDA/DMF(s)
  NDA #85-106
  ANDA #40-341

13. DOSAGE FORM Tablets for oral administration

- 14. <u>POTENCIES</u>
  7.5 mg/500 mg
  10 mg/650 mg
- 15. CHEMICAL NAME AND STRUCTURE

## Oxycodone Hydrochloride C<sub>18</sub> H<sub>21</sub> NO<sub>4</sub> . HCl



4,5α-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride

## Acetaminophen USP C<sub>8</sub>H<sub>9</sub>NO<sub>2</sub>; M.W. = 151.17

4'-Hydroxyacetanilide

## 16. RECORDS AND REPORTS 7/9/99 - Bioequivalence review, P. Nwakama.

7/30/99 - Labeling review #1, C. Park.

### 17. COMMENTS

Deficiencies were identified as follows:

Specifications of the raw material,
Process of manufacture,
Container and Closure,
In-process controls,
Specifications for the finish drug product, and
Stability.

## 18. CONCLUSIONS AND RECOMMENDATIONS

The application is deficient and is not recommended for approval. The response to all deficiencies will be considered a MAJOR amendment.

### 19. REVIEWER:

Mayra L. Piñeiro-Sánchez, Ph.D.

DATE COMPLETED: November 17, 1999 November 29, 1999 Contain Trade Secret,

Commercial/Confidential

Information and are not
releasable.

Cher Per 1 11/17/99

# CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 40-371

**BIOEQUIVALENCE** 

Acetaminophen and Oxycodone HCl Tablets 500 mg/7.5 mg & 650 mg/10 mg

ANDA# 40371A

Reviewer: Patrick E. Nwakama

File Name: 40371A.1100

Watson Labs, Inc. 16600 NW 54th Ave Submission Date: November 28,2000

## Review Of A Dissolution Amendment

## HISTORICAL BACKGROUND

November 9, 1998 -On the basis of its approved suitability petition (Docket #98P-0105/CP1, approved 11/6/98), the Endo requested a waiver of in vivo bioequivalence study requirements for its test combination product, Acetaminophen & Oxycodone HCl Tablets (500 mg/7.5 mg & 650 mg/10 mg) and submitted a comparative dissolution data on its test product and the reference listed drug (RLD), Percocet® 325 mg/5 mg tablet (Endo, NDA 85-106).

May 7, 1999 - Based on the suitability petition (Docket #98P-0105/CP1), Watson Lab requested a waiver of in vivo bioequivalence study requirements for its test combination product, Acetaminophen & Oxycodone HCl Tablets (500 mg/7.5 mg & 650 mg/10 mg) and submitted a comparative dissolution results on its test product and the reference listed drug (RLD), Percocet® 325 mg/5 mg tablet (Endo, NDA 85-106).

July 12, 1999 -The Division of Bioequivalence tentatively approved the two strengths of Watson's test product.

July 26, 1999 -Endo's ANDA (#40-341) for Percocet® (Acetaminophen & Oxycodone HCl Tablets 500 mg/7.5 mg & 650 mg/10 mg) was approved.

November 21, 2000 -The Agency requested Watson to conduct another set of comparative dissolution profiles using recently approved Percocet® 500 mg/7.5 mg and 650 mg/10 mg, tablets.

FORMULATION COMPARISON - Please refer to Table 1

## **COMMENTS**

- l. The drug is classified "AA" in the list of "Approved Drug Products with Therapeutic Equivalence Evaluation." The test drug product contains the same active ingredients, but in different concentrations, as the reference listed drug (Table I).
- 2. The Division of Bioequivalence has previously given tentative approval to Watson's Acetaminophen /Oxycodone HCl Tablets USP (500 mg/7.5 mg & 650 mg / 10 mg) based on comparative dissolution profiles of the test product and the RLD, Endo's Percocet® 325 mg/5 mg which was then the RLD. However, while the final FDA approval is still

pending, the DBE was informed that Endo's Percocet® 500 mg / 7.5 mg and 650 mg /10 mg have been approved as the RLD products. Consequently and at the request of the Division the firm has performed comparative dissolution profiles with the same dosage strengths of Percocet® as the RLDs.

3. The obtained  $F_2$  values were  $\geq 60$  suggesting strong similarity in dissolution profile between the test and reference products.

## RECOMMENDATION

- l. The Division of Bioequivalence agrees that the information submitted by Watson on its drug product, Acetaminophen /Oxycodone HCl Tablets USP (500 mg/7.5mg & 650 mg/10 mg) falls under 21 CFR Section 320.22(c). The waiver of in vivo Bioequivalence study for the test product is granted. From the bioequivalence point of view, Watson's Acetaminophen /Oxycodone HCL Tablets, 500 mg / 7.5 mg and 650 mg / 10 mg, are acceptable.
- 2. The dissolution testing conducted by Waston comparing its test drug products, Acetaminophen/Oxycodone Tablets, 500 mg / 7.5 mg and 650 mg /10 mg, lot #s PG 1571 and PF 1566, with Endo's Percocet® 500 mg / 7.5 mg and 650 mg /10 mg, lot #s PF-543A and ENK 452A, has been found acceptable.
- 3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability programs as specified on page 1236 of USP XXIV.

4. The current RLDs are not scored while both Watson's Acetaminophen/Oxycodone Tablets, 500 mg / 7.5 mg and 650 mg /10 mg tablets are scored. As per 1995 OGD MAPP 5223.2 and the approval summary from labeling, the scored tablets from Watson are acceptable.

Patrick E. Nwakama, Pharm.D.

Division of Bioequivalence Review Branch II

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Concur A Dale Conner, Pharm.D.

Director, Division of Bioequivalence

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Information and are not releasable.

11/28/00

	Table 2: In-Vitro COMPARATIVE DISSOLUTION TESTING							
Drug: Acetar	minophen 7 Ox	ycodone Hydrochlo	oride Tablets					
	Date: Novemb							
File Name: 4	10-371DW.110	00						
I. Condition	I. Conditions for Dissolution/Release Testing: USP METHOD							
USP XXIII		-	Medium: 0	.1 N HCl				
Apparatus: '	Type 2 (Paddle	2)	Volume: 90	00 mL	•			
RPM: 50	,	,	Tolerance:		45 min			
No. Units To	ested: 12		(Acetamino	phen / Oxycoo	done HCl)			
Reference D	rug: Percocet®		Assay Meth					
II. Results	of In Vitro Di	issolution/Release	Testing:[AC]	ETAMINOPH	IEN COMPONI	ENT]		
Sampling	Test Product	: Acetaminophen/O	xycodone	Reference Pro	oduct: Percocet®	Tablets		
Times	Lot No.: PG-	_		Lot No.: PF-	543A			
(min)	Strength: 500	0 mg / 7.5 mg		Strength: 500	0 mg / 7.5 mg			
<u> </u>	Mean %	Range	CV%	Mean %	Range	CV%		
15	104.6		1.2	100.8		2.1		
30	105.1	<del></del>	0.9	101.9	<del>_</del>	2.1		
45	105.0		1.0	102.0	<del></del>	2.2		
60	104.4		1.0	102.7	<del></del> 99.0 - 10.	1.6		
F2	104.4	102.0 10	75		77.0 · 10.			
Sampling	I .	: Acetaminophen/O	xycodone		oduct: Percocet®	lablets		
Times	Lot No.: PF-			Lot No.: ENK452A				
(min)	<del>+</del>	0 mg / 10 mg		Strength: 650 mg / 10 mg				
	Mean %	Range	CV%	Mean %	Range	CV%		
15	97.7	_ ^	2.3	96.6	<del>-</del>	4.8		
30	98.8		1.2	100.2		2.4		
45	98.7	_	1.1	101.6		2.1		
60	98.5		1.2	102.3	<b>4-</b> 10	1.7		
F2			78	3	· · · · · · · · · · · · · · · · · · ·			
II. Results	of In Vitro D	issolution/Release	Testing: [OX	CYCODONE	COMPONENT]			
Sampling	Test Product	: Acetaminophen/O	xvcodone	Reference Pr	oduct: Percocet®	Tablets		
Times	Lot No.: PG-		11) 0000110	Lot No.: PF-		100.00		
(min)	1	0 mg / 7.5 mg			0 mg / 7.5 mg			
	Mean %	Range	CV%	Mean %	Range	CV%		
15	101.2		2.8	99.3		2.1		
30	100.7	<del>-</del>	2.1	99.8	<u>-</u>	1.8		
45	100.7	<del>-</del>	2.2	99.0	<del></del>	2.2		
60	99.3	<del>-</del> -	<del></del>		<del>-</del>	<del></del>		
	77.3	シロロ .	2.1	98.8		1.6		
F2	<u> </u>	<del></del>	90					
Sampling		: Acetaminophen/O	xycodone	ł .	oduct: Percocet®	Tablets		
Times	Lot No.: PF-			Lot No.: ENK452A				
(min)	Strength: 650 mg / 10 mg         Strength: 650 mg / 10 mg							
	Mean %	Range	CV%		Range	CV%		
15	96.0		2.1	98.7		6. l		
30	95.4		1.7	101.2		2.1		
45	94.7		1.6	101.7		2.0		
60	93.6	90.9-7.	1.5	101.5	[	1.8		
F2			.60	)	_			
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## Acetaminophen and Oxycodone HCl Tablets 500 mg/7.5 mg & 650 mg/10 mg

ANDA# 40371

Reviewer: Patrick E. Nwakama

File Name: 40371DW.699

Watson Labs, Inc 16600 NW 54<sup>th</sup> Ave Submission Date: June 7, 1999 May 7, 1999

## Review of Dissolution Data and Waiver Requests

#### BACKGROUND

- The firm has requested a waiver of in vivo bioequivalence study requirements for its test combination product, Acetaminophen & Oxycodone HCl Tablets (500 mg/7.5 mg & 650 mg/10 mg).
- 2. The firm has also submitted a comparative dissolution results on its test product and the reference listed drug(RLD), Percocet<sup>R</sup> 325 mg/5 mg tablet(Endo, NDA 85-106).
- 3. The two strengths (500 mg/7.5 mg & 650 mg/10 mg) were found suitable for filing based on a suitability petition(Docket # + 98P-0105/CP1) approved on November 6, 1998, by the FDA.

## FORMULATION COMPARISON (Not to be released under FOI)

INGREDIENT	325 mg/5 mg Percocet <sup>R</sup> (White tablet)	500mg/7.5 mg <b>TEST</b>	650mg/10 mg TEST
Oxycodone HCl	5 mg	7.5 mg	10 mg
Acetaminophen	<del>-</del> '		
Microcrystalline		•	
Povidone,	-		1
Croscarmellose		3 D D	,
Corn Starch,			· —
Colloidal Silicon			-
Stearic Acid,	+		·
Magnesium Stearate	<del> </del>		
Sucrose	<u> </u>		
Total Weight			

#### IN-VITRO COMPARATIVE DISSOLUTION TESTING

Drug: Acetaminophen / Oxycodone Hydrochloride Tablets Dose Strength(s): 500 mg / 7.5 mg and 650 mg/10 mg

ANDA #: 40-371

2 - A.

Firm: Watson Pharmaceuticals, Inc.

#### Submission Date: June 7, 1999 File Name: 40-371DW.699 **USP METHOD** I. Conditions for Dissolution/Release Testing: USP XXIII Medium: 0.1 N HCl Apparatus: Type 2 (Paddles) Volume: 900 mL RPM: 50 Tolerance: 🚬 .n 45 min (Acetaminophen / Oxycodone HCl) No. Units Tested: 12 Assay Method: Reference Drug: Percocet® II. Results of In Vitro Dissolution/Release Testing: [ACETAMINOPHEN COMPONENT] Test Product: Acetaminophen/Oxycodone Tablets Reference Product: Percocet® Tablets Sampling Times Lot No.: PG-1571 Lot No.: EHL287A Strength: 325 mg/5 mg (min) Strength: 500 mg/7.5 mg Mean % Range CV% Mean % Range CV% 4.4 15 104.6 1.2 66.1 30 105.1 0.9 76.7 5.5 45 105.0 1.0 81.4 7.4 102.0-105.5 60 104.4 1.0 84.9 7.4 Sampling Test Product: Acetaminophen/Oxycodone Tablets Reference Product: Percocet® Tablets Lot No.: PF-1566 Lot No.: EHL287A Times Strength: 650 mg/10 mg Strength: 325 mg/5 mg (min) CV% CV% Mean % Mean % Range Range 15 97.7 2.1 30 98.8 1.7 45 98.7 1.6 60 98.5 1.5

II. Results of	of In Vitro Dissolu	ition/Release Testing	: [OXYCODO	ONE COMPONI	ENT	
Sampling	Test Product: A	cetaminophen/Oxyco	done Tablets	Reference Product: Percocet® Tablets		
Times	Lot No.: PG-15	71	Lot No.: EHL287A			
(min)	Strength: 500 m	ng/7.5 mg		Strength: 325 mg/5 mg		
	Mean %	Range	CV%	Mean %	Range	CV%
15	101.2	<del></del>	2.8	97.7	90.9-103.5	3.6
30	100.7		2.1	99.7	94.2-105.2	3.6
45	100.2		2.2	. 99.8	91.9-105.2	3.8
60	99.3	<del></del>	2.1	99.8	92.1-105.4	4.1
Sampling Test Product: Acetaminophen oxycodone Tablets			Reference Product: Percocet® Tablets			
Times	Lot No.: PF-15	66		Lot No.: EHL287A		
(min)	Strength: 650 m	ng/10 mg		Strength: 325 mg/5 mg		
	Mean %	Range	CV%	Mean %	Range	CV%
15	96.0	<del></del>	2.1			
30	95.4		1.7			
45	94.7		1.6			
60	93.6		1.5			

2.

### COMMENTS

- 1. The drug is classified "AA" in the list of "Approved Drug Products with Therapeutic Equivalence Evaluation."
- 2. The test drug product contains the same active ingredients, but in different concentrations, as the reference listed drug (Table I).
- 3. The test product and RLD met the USP dissolution specifications for Acetaminophen and Oxycodone HCl Tablets USP as outlined.
- 4. The Division of Bioequivalence has approved similar strength products from Endo Pharmaceuticals on 1/11/99. However, final approval from the Office of Generic Drugs is still pending.
- 5. The following  $f_2$  comparisons were performed:

	Test 500 mg/	Test 650 mg/	Ref. 325 mg/	Ref. 325 mg/
	7.5 mg	10 mg	5 mg	5 mg
Test 500 mg/7.5 mg	-/-	60/64	27/86	27/86
Test 650mg/10 mg	60/64	-/-	32/66	32/66
Ref. 325 mg/5 mg	27/86	32/66	-/ <del>-</del>	-/-
Ref. 325 mg/5 mg	27/86	32/66	-/-	-/-

### RECOMMENDATION

- 1. The Division of Bioequivalence agrees that the information submitted by Watson on its drug product, Acetaminophen /Oxycodone HCl Tablets USP (500 mg/ 7.5 mg & 650 mg/10 mg) falls under 21 CFR Section 320.22(c). The waiver of in vivo Bioequivalence study for the test product is granted. From the bioequivalence point of view, Watson's Acetaminophen /Oxycodone HCL Tablets, 500 mg/7.5 mg and 650 mg/10 mg, are acceptable.
- The dissolution testing conducted by Waston on its drug product, Acetaminophen/Oxycodone Tablets, 500 mg/7.5 mg & 650 mg/10 mg, lot # PG 1571 & PF 1566, has been found acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 900 mL 0.1 N HCl at 37°C using apparatus II (paddles) at 50 rpm. The test product should meet the following specifications:

Not less than of the labeled amount of acetaminophen and oxycodone in the dosage form is dissolved in 45 minutes.

Patrick E. Nwakama, Pharm.D. Division of Bioequivalence Review Branch II

RD INITIALED SNERURKAR FT INITIALED SNERURKAR

Date:

7/9199

Concur (

Dale Conner, Pharm.D.

Director, Division of Bioequivalence

# CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 40-371

## **ADMINISTRATIVE DOCUMENTS**

### DIVISION REVIEW SUMMARY

ANDA: 40-371

DRUG PRODUCT: Oxycodone Hydrochloride and Acetaminophen

FIRM: Watson Laboratories

**DOSAGE FORM:** Tablets

STRENGTHS: 7.5 mg/500 mg and 10 mg/650 mg

**CONTAINERS:** 

100's (200 cc) and 500's (750 cc)

### CGMP STATEMENT/EIR UPDATE STATUS:

Acceptable dated 3/2/00.

#### BIO INFORMATION:

Acceptable dated 7/12/99.

#### VALIDATION

No method validation required. Compendial products.

#### STABILITY

Lot nos. PG-1571/150,000 units and PF-1566/150,000 units were placed in accelerated (40°C/75%RH) and room temperature stability studies in the smallest and largest of the proposed marketing container configurations. The stability data appended are found to conform to the proposed stability specifications. Based upon the stability data submitted, the proposed 24 months expiration period should be granted.

The container/closure systems are described.

#### LABELING

Acceptable dated 10/2/00.

### STERILIZATION VALIDATION

N/A

### SIZE OF BIO/STABILITY BATCHES

Oxycodone Hydrochloride is manufactured by Noranco, DMF was found to be adequate on 3/19/99. No relevant revisions since last review.

Acetaminophen is manufactured by

DMF-was found to be adequate on 3/31/00.

Oxycodone Hydrochloride and Acetaminophen Tablets, demonstration lot no. PG-1571/ units and 10 demonstration lot no. PF-1566, units.	mg
PROPOSED PRODUCTION BATCH  BBR for the intended production batch size of and tablets are included.	
SPECIFICATIONS TO BE APPROVED:	
Oxycodone Hydrochloride USP	
2°C pectrum	
Acetaminophen 90%, Compac L	
-	
.18	
-	

## In-process Controls

Friability NMT 1% in 4 min

## FINISHED DRUG PRODUCTS:

Tests	Limits
Overedone HC!	
	PCD. NIMIT C 00

	Only one tablet may be 75.0-85.0% or 115.0%-125.0%
Assay (HPLC)	1
	oth)

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Test	Specification
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## RECOMMENDATION:

Recommend approbable letter to issue for Oxycodone Hydrochloride and Acetaminophen Tablets, 7.5 mg/500 mg and 10 mg/650 mg.

SIGNATURE:

DATE: November 8, 2000

V:\FIRMSNZ\WATSON\LTRS&REV\40371DS.doc

## RECORD OF TELEPHONE CONVERSATION

DATE: June 3, 1999

DRUG PRODUCT: Oxycodone and Acetaminophen

ANDA NUMBER: 40-371

COMPANY: Watson Labs

NAME OF COMPANY REPRESENTATIVE(S): Loren Gelber

NAME OF OGD REPRESENTATIVE(S): Nasser Mahmud

Telecon initiated by: Nasser Mahmud

COMPANY TELEPHONE: 305-624-1500

I called Loren to request the following:

Labeling comparison in the ANDA is done against Watson's previously approved product and not the reference listed drug. I asked her to submit a new side by side comparison of all labeling; using the reference listed drug by Endo labs and provide required number of copies for all labeling for the reference listed drug. Loren asked if the ANDA could be filed prior to receiving this info? I notified her that she should contact the labeling branch. If they decide that this type of info can be submitted during the review process, I will accept the ANDA for filing.

I also notified Loren that DMF authorizations for both active drug substances in the ANDA refer to Royce Labs and not Watson. DMF authorizations should be changed to reflect authorization to Watson labs. She said that Watson labs operates under both names, Watson and Royce, in United States. I told her that in that case, in future submissions, DMF authorization should reflect the name of the applicant to avoid this type of confusion. - She agreed and conversation ended.

# CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 40-371

## **CORRESPONDENCE**



A Subsidiary of Watson Pharmaceuticals, Inc.

November 28, 2000

Gary Buehler, Rh.D. Acting Director OGD, CDER, FDA Metro Park North II 7500 Standish Place Rockville, MD 20855 NDA ORIG AMENDMENT

3 0 2000

OGD

Re:

Oxycodone with Acetaminophen Tablets, 7.5/500mg and 10/650 mg

ANDA 40-371

Telephone Amendment

Dear Mr. Buehler,

This is in response to a telephone conversation with Ms. Kistra Scardina on Nov. 21, 2000 regarding our Oxycodone with Acetaminophen Tablet application (ANDA 40-371). In a FDA letter dated Aug. 14, 2000, OGD stated that "The Division of Bioequivalence has completed its review and has no further questions at this time." However, on Nov. 21, 2000, the Division of Bioequivalence requested that comparative dissolution profiles be performed with Percocet ® 7.5/500 mg and 10/650 mg tablets (reference) and Watson's 7.5/500 mg and 10/650 mg tablets (test) using USP dissolution conditions.

The requested comparative dissolution profile data are attached. The dissolution profiles for Percocet and Watson products are basically equivalent under the following dissolution parameters:

Medium: 0.1 N HCl, 900 ml

Apparatus 2; 50 rpm

Time: 15, 30, 45 and 60 minutes

We believe that we have addressed all FDA's concerns and request immediate approval of this application. Please direct any written communications regarding this ANDA to the address above. Additionally, I can be reached by phone at (909) 270-1400, Ext. 4332

or by fax at (909) 278-0967.

Ernest Lengle, Ph.D

Executive Director, Regulatory Affairs

## BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-371A

APPLICANT: Watson

DRUG PRODUCT: Acetaminophen and Oxycodone HCl, USP, Tablets 500 mg/7.5 mg & 650 mg/10 mg

The Division of Bioequivalence has completed its review and is requesting the following commitment.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs as specified in USP XXIV:

The dissolution testing should be conducted in 900 mL of 0.1 N HCl using USP Apparatus II (Paddle) at 50 rpm. The test product should meet the following specifications:

)) of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm. D.

Director

Division of Bioequivalence

Office of Generic Drugs

Center for Drug Evaluation and Research



A Subsidiary of Watson Pharmaceuticals, Inc.

September 11, 2000

Mr. Gary Buehler, Rh.D. **Acting Director** OGD. CDER, FDA Metro Park North II 7500 Standish Place Rockville, MD 20855

ORIG AMENDMENT

Reference: Oxycodone HCI and Acetaminophen Tablets

7.5 mg/500 mg and 10 mg/650 mg

ANDA #40-371 Fax Amendment

Dear Mr. Buehler:



This is in response to the FDA Fax Amendment letter dated August 14, 2000 regarding Oxycodone HCl and Acetaminophen Tablets 7.5 mg/500 mg and 10 mg/650 mg (ANDA 40-371). Our complete response is provided below. For ease of review, FDA's comments are in bold face followed by our response.

1. We acknowledge that in the event that the proposed time limit between the completion of blending and the beginning of compression is exceeded, you proposed to perform a test for potency and moisture. In addition, to these tests we recommend that blend uniformity analysis of the blend be performed.

As per your recommendation, the batch records for both the strengths have been revised to include the following statement: "If the one month time limit between completion of blend and the initiation of compression is exceeded, blend uniformity and moisture testing must be performed prior to compression". This information is provided in page 21, step 28 batch size) and in page 30, step 36 batch size) of the batch records. The revised batch records are provided in Exhibit 1.

2. The modification of the blend "Assay" to a single-tier acceptance criteria is adequate. However, the specifications were not modified and any reference to the samples being no larger than three-times the unit dosage was removed. Please submit updated copies that reflect the change in specification to , (mean of individual results) with an RSD of 5.0% for samples no larger that three times the unit dosage.

As per your recommendation, the test procedures and specifications for both the strengths have been revised to reflect the acceptance criteria for Blend Uniformity as NLT and NMT (mean of individual results) with an RSD of NMT for samples no larger than three times the unit dosage. The revised methods and specifications are provided in Exhibit 2.

3. The limit for "Largest individual unkown" is included in the finished product and stability Quality Control Reports but has been deleted from the methods. Please include and resubmit.

As per your recommendation, the finished product and stability method has been revised to include the limit for the largest individual unknown impurities. The revised methods are provided in Exhibit 3.

4. We acknowledge that finished product and stability limits have been set for

However, the method validation report does not include data for these impurities. Please submit.

As per your recommendation, the method validation report has been revised to include the data for /

impurities. The revised method validation report is provided in Exhibit 4.

5. The stability commitment should be modified to indicate that the first three production lots of each strengths will be placed on stability.

As per your recommendation, the stability commitment has been revised to indicate that the first three production lot of each strength will be placed on stability. The revised stability commitment is provided in Exhibit 5.

6. Labeling Deficiencies: CONTAINER – 100s & 500s

Please note that the innovator adopted a potency sticker program, which was approved by the Agency. This program is to caution the health practitioners about the multiple strengths of Oxycodone and Acetaminophen tablets. The stickers appear on the caps of the bottles of

the innovator for your reference. Please propose the potency sticker, as instructed above, and submit in final print.

As per your recommendation, we are providing 12 copies of the final printed potency stickers. The stickers are presented in Exhibit 6.

Please note that the final printed potency stickers provided include an additional strength of Oxycodone HCl and Acetaminophen Tablets, 5mg/325mg, ANDA #40-171 that was previously approved by the Agency on 10/30/97.

We believe that Watson has satisfactorily responded to all FDA's questions and concerns regarding this submission. If you have any additional questions or if I can assist you with the review of this amendment, please do not hesitate to contact me by telephone at (909) 270-1400 or by facsimile at (909) 278-0967.

Sincerely

Ernest Lengle, Ph.D.

Senior Director

Regulatory Affairs

38. Chemistry Comments to be Provided to the Applicant

ANDA: 40-371 APPLICANT: Watson Laboratories, Inc.

DRUG PRODUCT: Oxycodone HCl/Acetaminophen Tablets.
7.5 mg/500mg & 10 mg/650 mg

The deficiencies presented below represent FAX deficiencies.

## Deficiencies:

- 1. We acknowledge that in the event that the proposed time limit between the completion of blending and the beginning of compression is exceeded, you propose to perform a test for potency and moisture. In addition to these tests we recommend that blend uniformity analysis of the blend be performed.
- 2. The modification of the blend "Assay" to a singletier acceptance criteria is adequate. However, the specifications were not modified and any reference to the samples being no larger than three-times the unit dosage was removed. Please submit updated copies that reflect the change in specification to (mean of individual results) with a RSD of 5.0% for samples no larger than three times the unit dosage.
- 3. The limit for "Largest individual unknown" is included in the finished product and stability Quality Control Reports but has been deleted from the methods. Please include and resubmit.
- 4. We acknowledge that finished product and stability limits have been set for

and

However, the method validation report does not include data for these impurities. Please submit.

5. The stability commitment should be modified to indicate that the first three production lots of <u>each</u> strength will be placed on stability.

Vilagat Sagus.

Sincerely yours,

Sol

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEOUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

APPLICANT: Watson ANDA: 40-371

DRUG PRODUCT: Acetaminophen and Oxycodone HCl 500 mg/7.5 mg & 650 mg/10 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm. D.

Director

Division of Bioequivalence

Office of Generic Drugs

Center for Drug Evaluation and Research

# ARCHIVAL COPY



A Subsidiary of Watson Pharmaceuticals, Inc.

March 17, 2000

Gary Buehler, R. Ph. Acting Director OGD, CDER, FDA Metro Park North II 7500 Standish Place Rockville, MD 20855 AC AMENDORA

RE: Oxycodone HCl with Acetaminophen Tablets, 7.5 mg/500 mg & 10 mg/650 mg ANDA 40-371

Dear Mr. Buehler:

This is in response to a FDA deficiency letter dated Dec. 14, 1999 regarding Oxycodone HCl with Acetaminophen Tablets, 7.5 mg/500 mg & 10 mg/650 mg (ANDA 40-371). For ease of review, FDA's comments are in bold face followed by our response.

1. The water used during manufacturing should be included as part of the components and composition statement. Please modify and resubmit.

The water used during manufacturing is included in the Qualitative and Quantitative Composition Statements for both strengths (see Exhibit 1). In addition, the functional category of all the excipients used in the formulation is identified.

2. Regarding the specifications for the raw materials:

√a.

k in

√b.

Contain Trade Secret,

Commercial/Confidential

Information and are not releasable.

3/17/00

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7. Regarding stability:

d. Please modify your post approval commitment to complete the necessary stability testing to include the 10 mg/650 mg strength.

The post approval commitment is revised (see exhibit 16).

- ✓a. In you room temperature stability protocol you state that "Staring 12 months after packaging of the first full-scale batch, or after approval of the ANDA whichever is later, one batch of each strength per year thereafter will be sampled for RT stability". In order to be in compliance with the Agency's Stability Guidelines please modify this sentence to clearly indicate that once the necessary studies have been completed in the first three commercial production batches for each strength, one batch per year for each strength will be placed on RT stability. In addition, modify your test stations to reflect initial testing of stability samples.
- b. In your statement concerning extension of the expiration dating please indicate that "The long-term room temperature stability data of at least three production batches may be used to extend the expiration dating".
- The tests for friability and physical appearance are included in you stability report but are missing form your stability protocol. Please modify you protocol in include these tests.



Please modify your stability protocol and stability commitment and resubmit.

The stability protocol and stability specifications for production lots document has been revised as per the above recommendations (see exhibit 17). Stability data are provided in Exhibit 18.

- C. In addition to the deficiencies presented above, please note and acknowledge the following:
- 1. It is recommended that the function of all excipients used in your formulation be identified. Please provide a statement that includes this information.

The functional category of all the excipients used in the formulation is identified, and a statement with this information is included (see Exhibit 1).

2. We note that the tests for dissolution, total impurities, appearance of lot #PG-15-71 (100s, p. 956; 500s, p.957) were not performed in accordance with the test stations as outlined in your proposed stability protocol. For future studies, we request you follow the stability protocol in your application.

We acknowledge that except for the Chromatographic Purity Analysis, all testing for the one month accelerated stability was completed on time. Chromatographic Purity for one and two months accelerated conditions were tested together. In the future, we commit to follow the submitted stability protocol in our application.

## Labeling Deficiencies:

1. CONTAINER - 100s & 500s

We ask that you increase the prominence of the expression of the strength for 7.5 mg/500 mg tablets by changing print color, boxing and/or other means.

The prominence of the expression of the the strength for 7.5mg/500 tablets has been increased per FDA recommendation.

### 2. INSERT

#### a. GENERAL

Please note in the last approved labeling of Percocet,, the term "narcotic" has been replaced with "opioid". We ask that you revise the labeling accordingly throughout the text.

#### b. TITLE

We encourage the relocation of "Rx only" to appear beneath the title



b. Description - Third paragraph (The oxycodone component ...):

Oxycodone, 14-hydroxydihydrocodeinone, is a semisynthetic opioid agonist which occurs as a white, ...

c. CONTRAINDICATIONS - Revise to read:

....acetaminophen, or any other components of this product.

d. PRECAUTIONS - Pregnancy:

Revise this subsection to read "Usage in Pregnancy".

F. DRUG ABUSE AND DEPENDENCE

Oxydocone and acetaminophen tablet is a ... [singular]

g. DOSAGE AJND ADMINSTATION - Add the following at the end of this section

...needed for pain. The total daily dose of acetaminophen should not exceed 4 grams and the maximal daily dose is as follows:

	Maximal Daily Dose
5 mg/325 mg	12 tablets
7.5 mg/500 mg	8 tablets
10 mg/650 mg	6 tablets

#### h. HOW SUPPLIED

a. We note that the description of the 5 mg/325 mg tablets has been revised from the one appearing in your last approved labeling for this strength. Please comment.

The insert was revised 11/97. At that time, the description of the 5 mg/325 mg strength was given as "white, scored, round tablets debossed Watson on one side and bisect on the other side."

This is the current description.

b. Add "(See USP)" to the storage requirement to read "...(59F-86F). [See USP]"

Please revise your labels and labeling, as instructed above, and submit in final print.

All labels and insert have been revised as requested. A summary of changes made to Watson Laboratories Product Insert is attached (see Exhibit 19). In addition, final printed copies of labels and inserts are included also.



We believe that all questions and/or concerns expressed by FDA in the Dec. 14, 1999 deficiency letter have been resolved.. If you have any additional question, please reach me by phone at (909) 270-1400 or by fax at (909) 278-0967.

Sincerety,

Ernest Lengle, Ph/

Director

Regulatory Affairs

BIOEOUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-371 APPLICANT: Watson

DRUG PRODUCT: Acetaminophen and Oxycodone HCl

500 mg/7.5 mg & 650 mg/10 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm. D.

Director

Division of Bioequivalence

Office of Generic Drugs

Center for Drug Evaluation and Research

Watson Laboratories, Inc. Attention: Loren Gelber, Ph.D. 16600 NW 54<sup>th</sup> Avenue Miami, FL 33014 JUN 23 1999

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to your correspondence dated June 7, 1999.

NAME OF DRUG: Acetaminophen and Oxycodone Hydrochloride Tablets, 500 mg/7.5 mg and 650 mg/10 mg

DATE OF APPLICATION: May 7, 1999

DATE (RECEIVED) ACCEPTABLE FOR FILING: May 10, 1999

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Tim Ames Project Manager (301) 827-5849

Sincerely yours,

I Luwey of Mealey

Robert L. West, M.S., R.Ph.

Director

Division of Labeling and Program Support Office of Generic Drugs

Center for Drug Evaluation and Research



A Subsidiary of Watson Pharmaceuticals, Inc.

May 7, 1999

Office of Generic Drugs

Center for Drug Evaluation and Research FOOD AND DRUG ADMINISTRATION

Document Control Room

Metro Park North II

7500 Standish Place, Room 150

**ROCKVILLE MD 20855-2773** 

NEW CORRESP

Reference:

ANDA 40-371

Oxycodone and Acetaminophen Tablets 7.5 mg/500 mg and 10 mg/650

mg

Gentlemen:

This is response to a telephone call received June 3, 1999 from Project Manager Nasser Mahmud of your office. As requested, labeling side-by-side comparison with the most recent approved labeling of the reference product, Percocet Tablets, is enclosed.

We trust that this information will be sufficient for the Agency to accept and file this application.

Sincerely,

WATSON LABORATORIES, INC.

Loren Gelber, Ph.D. -

Vice President Regulatory Compliance, Miami





A Subsidiary of Watson Pharmaceuticals, Inc.

May 7, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
ROCKVILLE MD 20855-2773

### Gentlemen:

Watson Laboratories, Inc. is submitting an Abbreviated New Drug Application under section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Oxycodone and Acetaminophen Tablets 7.5 mg/500 mg and 10 mg/650 mg. The basis of this submission is a citizen's petition Please note that Royce Laboratories became a wholly owned subsidiary of Watson Pharmaceuticals in April 1997 and is now doing business as Watson Laboratories, Inc. Miami Florida. Due to this transition, the documents in this application may contain the Royce name, the Watson name, or both names.

This application is organized as suggested in the Guidance for Industry – Organization of an ANDA, OGD #1 Revision 1, February 1999. The archival (blue) copy contains two volumes, The Chemistry Section (red) copy contains two volumes, and the Bioavailability Section (orange) copy contains one volume.

Sincerely,

WATSON LABORATORIES, INC.

Loren Gelber, Ph.D.

Vice President Regulatory Compliance Miami



38. Chemistry Comments to be Provided to the Applicant	
ANDA: 40-371 APPLICANT: Watson	
DRUG PRODUCT: Oxycodone HCl/Acetaminophen 7.5 mg/500 mg & 10 mg/650 mg	
The deficiencies presented below represent MAJOR deficiencies.	
A. Deficiencies:	
<ol> <li>The water used during manufacturing should be included as part of the components and composition statement. Please modify and resubmit.</li> </ol>	
2. Regarding the specifications for the raw materials:	
a.	
b. g	
<b>3</b>	
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c.	
2 . Daniel de la company de	
3. Regarding your process of manufacture:	
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•	
C. water uses, as and, so so .	

4. Regarding your container and closure:

Page(s)

Contain Trade Secret,

Commercial/Confidential

Information and are not releasable.

b.

c.

d.

ine ase ct lity

# 7. Regarding stability:

- e. Please modify your post approval commitment to complete the necessary stability testing to include the 10 mg/650 mg strength.
- a. In your room temperature stability protocol you state that "Starting 12 months after packaging of the first full-scale batch, or after approval of the ANDA, whichever is later, one batch of each strength per year thereafter will be sampled for RT stability". In order to be in compliance with the Agency's Stability Guidelines please modify
- this sentence to clearly indicate that once the necessary studies have been completed in the first three commercial production batches for each strength, one batch per year for each strength will be placed on RT stability. In addition, modify your test stations to reflect initial testing of stability samples.
- b. In your statement concerning extension of the expiration dating please indicate that "The longterm room temperature stability data of at least

- three production batches may be used to extend the expiration dating".
- c. The tests for friability and physical appearance are included in your stability report but are missing from your stability protocol. Please modify your protocol to include these tests.

Please modify your stability protocol and stability commitment and resubmit.

- C. In addition to the deficiencies presented above, please note and acknowledge the following:
  - 1. It is recommended that the function of all excipients used in your formulation be identified. Please provide a statement that includes this information.
  - 2. We note that the tests for dissolution, total impurities, for the one month samples from the accelerated study of lot #PG-1571 (100s, p. 956; 500s, p. 957) were not performed in accordance with the test stations as outlined in your proposed stability protocol. For future studies, we request you follow the stability

Sincerely yours,

Florence S. Fang

Director

protocol in your application.

Division of Chemistry II Office of Generic Drugs

Center for Drug Evaluation and Research

Day w 2/10/99